UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,895	02/16/2001	Luiz Belardinelli	MBHB00-081-A	4211

7590 08/14/2002

A. Blair Hughes
McDonnell Boehnen Hulbert & Berghoff
32nd Floor
300 S. Wacker Drive
Chicago, IL 60606

EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1638	9

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/785,895	Applicant(s) BELARDINELLI ET AL.	
	Examiner Mary Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 16 February 2001 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for design and administration of A2B antagonists to retinal cells in culture, does not reasonably provide enablement for design and administration of A2B antagonists to any cell in any whole organisms for the claimed therapeutic benefits. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons of record as set forth in the previous Official Action mailed 11/06/01.

Applicant's arguments filed 3/28/02 have been fully considered but they are not persuasive.

The amendments to claims 1, 3, 5, 11, 12 and 14 has not changed the breath of the claimed invention drawn to methods of inhibiting the proliferation of mammalian cells that express an A2B adenosine receptor comprising administering a therapeutically effective amount of an A2B adenosine receptor antagonist to the mammalian cells, whereby the proliferation of

cells is inhibited. Claims 16-18 have been newly added since they are drawn to assay methods including testing samples of human retinal endothelial cells which read on administration to retinal endothelial cells *in vivo*.

The specification as filed teaches by way of example administration of the A_{2B} antagonists JW-V1-08 and 3-N-propylxanthine (selective) and NECA (non-selective) in human retinal endothelial cells (HREC cells) in culture. The specification teaches prophetic design of other A_{2B} antagonists and use in other cell types, including administration to a whole organism for therapeutic purposes. The art references cited in the previous Official Action taught administration of A_{2B} antagonists to cells in culture, but does not support an expectation of success for design of any A_{2B} antagonist for administration to cells in whole organisms as broadly claimed.

While the specification is enabling for design of A_{2B} antagonists for administration to cells in culture, neither the specification nor the art provide sufficient guidance for the design and/or administration of any A_{2B} antagonist for cells in a whole organism, as presently claimed. The art teaches that the A_{2B} receptor has been identified in many different cell types in the whole organism. The claims broadly read on administering "a therapeutically effective amount of an A_{2B} adenosine receptor antagonist to the mammal" and thus reads on administration to any mammal.

Response to Arguments

Applicant first points out that the test for enablement must include consideration of the factors presented in *In re Wands*, 858 f.2d 731 (Fed. Cir. 1988) and MPEP 2164.01. It is noted that the *Wands* factors were considered in the previous Official Action and will be further discussed herein.

Applicant next argues that "the specification provides considerable guidance to enable a skilled artisan to make and use an A_{2B} adenosine receptor antagonist for inhibiting the proliferation of mammalian cells that express an A_{2B} adenosine receptor." However, as argued in the previous rejection, specific A_{2B} agonists and antagonists were not available in the prior art by traditional design methods taught by Klotz et al. and Kim et al. for instance. These references taught that a specific agonist and/or antagonist of the A_{2B} isoform was still needed and they implied that it was difficult to achieve. The instant specification does not teach any specific A_{2B} isoforms that are known to be useful for *in vivo* administration for the therapeutic functions claimed. Therefore, as argued previously, the specification as filed does not provide substantial guidance for making and using A_{2B} antagonists as asserted by Applicant.

Applicant states that "[t]he Federal Circuit has found that data showing the successful use of compounds as antitumor substances in tumor model systems were sufficient to enable the use of those compounds as anticancer drugs in animals....As established by the Federal Circuit, "if the art is such that a particular model is recognized as correlating to a specific condition then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate."" MPEP 2111.01 teaches that the claims as written must be given their broadest

reasonable meaning during the time of examination. As pointed out in the previous Official Action and above, the claims read on a broad scope of possible A_{2B} antagonists for administration to any mammalian cell type (thus via any route of administration) in any mammal. For the breath of claimed antagonists (of any type, nucleic acid, protein, small molecule) it was argued in the previous Official Action that there is a high level of unpredictability in the art for any gene therapeutic or therapeutic drug administration to a whole organism, and in view of the lack of guidance in either the specification or the prior art for design and use (ie. administration for the desired therapeutic results) one of skill in the art would necessarily practice an undue amount of experimentation to make and use the breath of the claimed invention. The correlation of a particular art recognized model for a particular therapeutic effect is determined on a case-by-case basis. The finding of the courts that certain tumor models were sufficient in one circumstance for use of the administered therapeutic agents in humans, does not correlate to the instant invention. The instant invention broadly embraces administration of any type of A_{2B} antagonist to any cell in any mammal for the claimed functions. The claims do not solely embrace administration to tumors as in the cited case law.

Applicant further asserts that human retinal endothelial cells used in the working examples of the instant application could be used as a predictive model for in vivo activity. Applicants state that "[t]he Office Action has not provided evidence that a human retinal endothelial cell models, as used int eh working examples of the instant application, do not correlate with inhibition of cell proliferation in mammals. The Office Action has only provided

general bald assertions that do not address the model used in the working examples. Absent evidence to the contrary, the Examiner must provide evidence...."

In response, again, the claims are drawn broadly to any administration of any agonist to any cell type in any mammal. Therefore, when weighing the working examples provided in the specification against the high level of unpredictability in the art (the factors considered unpredictable argued in the previous Official Action), it was determined that the teachings of the specification do not correlate to the breath of the claimed invention. The use of the human retinal endothelial cells as described in the specification with particular antagonists would be most closely predictive of direct administration of the demonstrated agonists in the retina. However, the prior art does not teach that this is a substantial art recognized model for the claimed invention. Note Cao (Int. J. Of Biochem. And Cell Biol., 2001, vol. 33, pages 357-369). Who teach that even after the filing of the instant invention, there is a high level of unpredictability in administering inhibitors in vivo for antiangiogenic therapy. They state in the abstract that "[o]ther disadvantages of the antiangiogenic protein therapy include repeated injections, prolonged treatment, transmission of toxins and infectious particles, and high cost for manufacturing large amounts of protein molecules." Note also Lahdenranta et al. (PNAS, Vol. 98, Issue 18, pages 10368-10373, Aug. 28, 2001) who taught in the discussion section of the reference what is know about the pathogenesis of neovascularization in ischemic retinopathies and the many variables involved in the development of the retina over time. Therefore, based on such knowledge, one skilled in the art would have understood at the time the invention was made

that administration of A_{2B} antagonists to the retina *in vivo* would have had many considerations not accounted for by a particular cell in cell culture which is stabilized at one stage. In view of these newly cited teachings, one of skill in the art would not have recognized that the teachings of the instant specification correlate to administration the breath of antagonists claimed to any mammal as claimed.

Therefore, although further research and development is allowed as long as it is routine to develop an invention further, one of skill in the art would have recognized that in the instant case, and undue amount of experimentation would have been necessary to make and use the breath of the claimed invention.

Although the specification teaches that some A_{2B} antagonists were known at the time the invention was made, the argument was raised previously that these antagonists were not necessarily A_{2B} specific, and thus would bind other types of adenosine receptors. Therefore, guidance is not taught in the specification for use of the stated antagonists for the A_{2B} specific functions claimed.

In regards to claims 7 and 8, the cited references do not correlate to the instant claims for antisense and ribozymes to A_{2B} since antisense use in vivo must be evaluated on an antisense-by-antisense basis. Therefore, success of antisense to VEGF, for instance, *in vivo* does not correlate to an expectation of the mechanical success and generation of specific treatment effects expected from an A_{2B} specific antisense or ribozyme. Similarly, FDA approval of one antisense for one

treatment circumstance does not correlate to development of antisense to other target genes for other specific treatments.

Finally, the following references are added to support the teachings of Branch and Flanagan:

There is a high level of unpredictability known in the antisense art and the related ribozyme art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense or ribozyme delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous

injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense or ribozyme specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an

RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of any A_{2B} antisense or ribozyme molecule *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense or ribozyme molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense or ribozyme molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects.

These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

3. The closest prior art to claims 16-18, Grant et al. and Grant et al. in view of Kemp et al., Kim et al. and Klotz et al. was overcome by Applicant in filing a declaration according to *In re Katz* showing that the Grant et al. reference was Applicants own work, published less than a year before the priority date of the instant Application. The claims are further free of the prior art since although the art taught the need for A_{2B} specific agonists and antagonists (Kim et al., Klotz et al. and Kemp et al.), the art did not specifically teach the motivation for testing in human retinal endothelial cells as instantly claimed. In regards to claims 1-15, the prior art did not teach nor fairly suggest administration of A_{2B} agonists and antagonists for the functions claimed.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

M. M. Schmidt
August 12, 2002

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.